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EVALUATION OF THE CARCINOGENIC POTENTIAL OF ***PROPANIL***

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FINAL REPORT

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HEALTH EFFECTS DIVISION
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EXECUTIVE SUMMARY

On May 9, 2001, the Cancer Assessment Review Committee (CARC) of the Health Effects Division (HED) of the Office of Pesticide Programs met to evaluate the carcinogenic potential of propanil. The studies evaluated included combined chronic toxicity and carcinogenicity studies in Wistar (1972) and Sprague-Dawley rats (1994) and in CD-1 mice (1983; 1994) .

The earlier studies with Wistar rats and CD-1 mice were considered to be unacceptable because of study deficiencies and inadequate dosing to test the carcinogenic potential of propanil. Since then, acceptable studies in Sprague-Dawley rats and Crl:CD-1 (ICR) BR mice were submitted by the registrant. In the 1994 rat study, Sprague Dawley rats (50/sex/dose) were fed diets containing 0, 200, 600, or 1800 ppm of propanil (0, 9, 27.7, or 88 mg/kg/day for males and 0, 11.3, 38.3, or 145 mg/kg/day for females, respectively) for 104 weeks. In the 1994 mouse study, propanil was administered to 60 Crl:CD-1 (ICR) BR mice/sex/dose at dietary levels of 0, 500, or 1000 ppm (0, 74.9, 150 mg/kg/day for males and 0, 88.6, 174 mg/kg/day for females, respectively) for up to 104 weeks. For both rat and mouse studies, an additional 20 animals/sex/dose were designated for interim sacrifice at week 52.

The CARC concluded that:

- **In Sprague-Dawley rats, there was a treatment-related increase in testicular adenomas** because: 1) There was a statistically significant positive trend and a statistically significant increase by pair-wise comparisons of the 600 and 1800 ppm dose groups with the controls for testicular interstitial cell adenomas in males (21% and 72%, respectively). 2) The incidences of these tumors in both dose groups were outside the range for the historical controls (0%-11%), and 3) These tumors were associated with an increased incidence of minimal interstitial cell hyperplasia. There was a difference of opinion among the Committee members regarding whether the highest dose in male rats was adequate or excessive. Decreased body weight gains (30% decrease compared to controls at week 13) and a marked increase in methemoglobin level (MeHb; range: 84%-132% increase over the course of study) were considered by some Committee members to be indicative of excessive toxicity while the remaining members were of the opinion that despite these changes, there were no clinical signs of toxicity and survival of the animals was not affected by the treatment.

  In females, there was a statistically significant positive trend and a statistically significant increase by pair-wise comparison of the 1800 ppm dose group with the controls for hepatocellular adenomas. The incidence of these tumors (13%) was outside the historical control range (0%-2%). The non-neoplastic changes in the liver were not severely adverse. **However the CARC determined that these tumors occurred at an excessively toxic dose based on decreased body weight gain (42% decrease compared to controls at week 13) and a marked increase in MeHb level (range: 106%-196%**

increase over the course of study).

Although there was a borderline increasing trend, there was no significant increase by pairwise comparisons of the 600 and 1800 ppm dose groups with the controls for endometrial polyps. The increased trend was considered by the CARC to be skewed because not all animals in 200 and 600 ppm dose groups were microscopically examined. The changes in the uterine wall were not severely adverse. Moreover, the endometrial polyps are not tumors but are considered simply as a proliferative response of the endometrium to the damaging effects of steroid sex hormones.

The CARC concluded that the testicular tumors observed in male rats in this study were treatment-related. There was no treatment-related increase in tumors in female rats.

! **In Crl:CD-1 (ICR) BR mice, there was a treatment-related increase in commonly occurring malignant lymphomas in females** as evidenced by a statistically significant positive trend and a statistically significant increase by pair wise comparison of the 1000 ppm dose group with the controls for malignant lymphomas.. There was an increase in the incidence of malignant lymphomas from controls in the high dose group only. Usually the CARC prefers historical control data from the performing laboratory of same study duration and performed within two years of the study under review. In this case the historical control data from the performing laboratory was based on only one study of comparable duration of 24 months. The historical control data from 4 other studies from the same laboratory was for 18 months. Therefore, the CARC considered historical control data cited by the registrant, published between 1982-1995, from different laboratories which ranged from 0%-28%. The incidence of 17% at the high-dose was within this historical control range. Moreover, this tumor occurs spontaneously in this sex and strain of mice. Therefore, the finding of malignant lymphomas at the high-dose was considered by the CARC to have a limited impact on the overall conclusion regarding the weight-of-the-evidence for the carcinogenic potential of propanil. No treatment-related tumors were observed in male mice.

The highest dose level tested was considered by the CARC to be adequate and not excessive because there were no treatment related adverse effects on the body weight gain, non-neoplastic histopathological findings or survival of the mice. However, there was an increase in MeHb levels, relative spleen weights and blue coloration of extremities in both sexes.

! A battery of pre-1991 acceptable Mutagenicity assays indicated that propanil was not genotoxic. No new studies were requested by the Committee.

! No mode of action studies related to the mechanism of tumor induction in rats or mice were available. Propanil causes anemia in laboratory animals. The mode of action for

methemoglobinemia involves hydroxylation of propanil to form N-hydroxyaniline which oxidizes hemoglobin to form methemoglobin.

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the CARC classified propanil into the category **"Suggestive evidence of carcinogenic potential by all routes of exposure, but not sufficient to assess human carcinogenic potential."** There was an increase in benign tumors in male rats. But considering the non-mutagenicity of propanil the available evidence for carcinogenicity did not reach the level of concern associated with category "Likely to be carcinogenic in humans". The Committee's decision was based on the following weight-of-the-evidence considerations:

1. Propanil induced testicular interstitial cell adenomas in male rats. The hepatocellular adenomas in female rats occurred only at an excessively toxic dose. The increase in commonly occurring malignant lymphomas in female mice added little to the overall weight of evidence for the carcinogenic potential of propanil.

2. Propanil was not genotoxic in a battery of acceptable mutagenicity assays.

The dose-response assessment is not indicated for agents when the evidence is "suggestive".

I. INTRODUCTION

On May 9, 2001, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of Propanil. At this meeting, information/data relevant to this review were presented by Dr. William Sette of the Toxicology Branch. These include chronic/carcinogenicity studies in Wistar and Sprague-Dawley rats and in CD-1 mice, metabolism, genetic toxicology, subchronic and chronic toxicity studies and data on structurally-related compounds. No mode of action studies related to the mechanism of tumor induction in rats or mice were available for review.

II. BACKGROUND INFORMATION

Propanil, N-(3,4-dichlorophenyl) propanamide, [CAS No. 709-98-8; PC Code 028201], is used as a postemergence contact herbicide. It is registered for use on grains, including rice, wheat, barley, and oats, and on peanuts, soybeans, grasses, and ornamental turf. There are food tolerances on the grains and on a variety of animal species that feed on grasses, including cattle, goats, hogs, and chickens.

Available formulations include emulsifiable concentrates, liquid and dry flowable, low volume, and ultra low volume formulations. There are no residential uses.

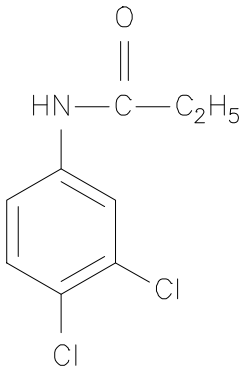

Figure 1. Propanil

III. EVALUATION OF CARCINOGENICITY STUDIES

The earlier studies with Wistar rats and CD-1 mice were considered to be unacceptable because of study deficiencies and inadequate dosing to test carcinogenic potential of propanil. Since then, acceptable studies in Sprague-Dawley rats and Crl:CD-1 (ICR) BR mice were submitted by the registrant. All available studies are summarized below.

1. Combined Chronic Toxicity/Carcinogenicity Study with Propanil in Wistar Rats

Reference: Anonymous. (1972). Toxicological Study on the Effects of Adding Stam F-34 to the Diet of Rats for a Period of 2-Years. Medical College of Virginia. HED Doc. No. 007559 **MRIDs 00036089; 00015419; 00134002.**

A. Experimental Design

A 2-year dietary study in Wistar rats (1972; MRIDs: 00015419) was available for review. In this study, groups of 25 rats/sex were administered propanil as STAM F-34 at 0, 100, 400 or 1600 ppm in the diet for a period of 2 years.

B. Discussion of Tumor Data

There was no treatment related increase in tumors noted.

C. Non-Neoplastic Lesions

No treatment-related increase in non-neoplastic lesions was noted.

D. Adequacy of the Dosing for Assessment of Carcinogenicity

The study was rated as supplementary because of lack of clinical chemistry analysis, inadequate histopathological examination and insufficient number of animals used in this study. The dosing was determined to be inadequate to test the carcinogenic potential of propanil.

2. Combined Chronic Toxicity/Carcinogenicity Study with Propanil in Sprague Dawley Rats

Reference: Propanil Technical, Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats (1994). Huntingdon Research Centre, Ltd., Cambridgeshire, England, for The Propanil Task Force, Sterling, Virginia. Study No. PTF 3, dated 7/1/94. **MRID 43303201**

A. Experimental Design

In this combined chronic toxicity/carcinogenicity study, Sprague Dawley rats (50/sex/dose) were fed diets containing 0, 200, 600, or 1800 ppm of propanil (0, 9, 28, or 88 mg/kg/day, males; 0, 12, 38, or 145 mg/kg/day, females) for 104 weeks. An additional 20 rats/sex/dose were designated for interim sacrifice at week 52.

B. Discussion of Tumor Data

Increased incidences of testicular interstitial cell adenomas in male rats and hepatocellular adenomas in female rats were observed.

1. Testicular Interstitial Cell Adenomas

The incidence and the statistical analyses of the testicular interstitial cell adenomas are shown in Table 1.

Table 1. Male Rats: Testicular Interstitial Cell Tumor Rates [+] and Peto's Prevalence Test Results (Brunsman, 2001)

	Dose (ppm)			
	0	200	600	1800
Incidence of adenomas	3/38 (8%)	3/34 (9%)	8/38[A] (21%)	29/40 (72%)
p =	0.000**		0.046*	0.000**

+ Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor
A- First tumor in an animal that died on study observed at week 86, dose 600 ppm.
Note: Interim sacrifice animals are not included in this analysis. There was one testes interstitial cell tumor in an interim sacrifice animal in the 600 ppm dose group.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level;If *, then $p < 0.05$. If **, then $p < 0.01$.

Male rats had a significant increasing trend at $p < 0.01$, and significant differences in the pair-wise comparisons of the 600 ppm (at $p < 0.05$) and 1800 (at $p < 0.01$) ppm dose groups with the controls, for testes interstitial cell adenomas. The incidence of testicular interstitial cell adenomas in 10 historical control studies ranged from 0-11%. Thus the incidences for both the 600 ppm and 1800 ppm rats were outside this range. **CARC concluded the tumors at both the 600 and 1800 ppm doses were treatment-related.**

There was difference of opinion among Committee members regarding whether the highest dose (1800 ppm) in male rats was adequate or excessive. The decreased body weight gains (30% decrease compared to controls at week 13) and a marked increase in methemoglobin level (MeHb; range: 84%-132% increase over the course of study) were considered by some members of the Committee to be indicative of excessive toxicity while the remaining members were of the opinion that despite these changes there were no clinical signs of toxicity and survival of the animals was not adversely affected.

2. Liver Adenomas

The incidences and the statistical analyses of the liver adenomas in female rats are shown in Table 2.

Table 2. Female Liver Tumor Rates [+] and Peto's Prevalence Test Results (Brunsman, 2001)

	Dose (ppm)			
	0	200	600	1800
Incidence of Adenomas #	1/36[A] (3%)	0/40 (0%)	1/39 (3%)	6/47 (13%)
p =	0.002**			0.049*

+ Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor in an animal that died on study.
#No liver carcinomas were observed in female rats.
A First liver adenoma observed at week 79, dose 0 ppm.

Note: Interim sacrifice animals are not included in this analysis. There were no liver adenomas in any interim sacrifice animals.

Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Female rats had a significant increasing trend at $p < 0.01$, and a significant difference in the pair-wise comparison of the 1800 ppm dose group with the controls at $p < 0.05$, for liver adenomas. The historical control range for female hepatocellular adenomas from 10 studies

ranged from 0-2%. Thus, the incidence at the high dose was outside the historical control range. **However, CARC determined that these tumors occurred at an excessively toxic dose as evidenced by decrease in body weight gain (42% decrease compared to controls at week 13) and a marked increase in MeHb level (range: 106%-196% increase over the course of study) in female rats.**

For males, there was no dose-related increase in the incidence of hepatocellular adenomas or carcinomas. The incidences in males at 0, 200, 600 and 1800 ppm doses, respectively, were as follows: adenomas : 0, 3 [6%], 0 and 0; carcinomas: 1[2%], 0, 3[6%], and 0.

3. Endometrial Polyps

The incidences and the statistical analyses of the endometrial polyps are shown in Table 3.

Table 3. Propanil - Sprague-Dawley Rat Study

Female Uterine Endometrial Polyp Rates[+] and Peto's Prevalence Test Results (p values)-(Brunsman, 2001)

	Dose (ppm)			
	0	200	600	1800
Endometrial Polyps	3/68	0/39#	3/37#	9[a]/70
(%)	(4)	(0)	(8)	(13)
p =	0.053	-	0.211	0.069

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor.

#Only those animals found dead or sacrificed in extremis, or those with macroscopic findings in the uterus, were examined microscopically in these dose groups.

[a]First endometrial polyp observed at week 52, dose 1800 ppm. in an interim sacrifice animal.

Note: Significance of trend denoted at control; onSignificance of pair-wise comparison with control denoted at dose level. If *, then $p < 0.05$. If **, then $p < 0.01$.

The statistically significant borderline increasing trend for endometrial polyps was of limited value because not all animals in the 200 and 600 ppm dose groups were examined. **There was no significant increase by pairwise comparison of the 1800 ppm dose group with the controls for**

endometrial polyps. Moreover, the endometrial polyps are not tumors but are considered simply as a proliferative response of the endometrium to the damaging effects of steroid sex hormones. Therefore, the CARC determined that there was no need to examine the remaining animals in the 200 and 600 ppm dose groups.

C. Non-Neoplastic Lesions

The treatment related non-neoplatic lesions of the liver, testes, and female reproductive organs are discussed below.

Liver changes observed were as follows: At 600 and 1800 ppm, there was granulomatous inflammation (Minimal: F: 10/50 and 40/50, respectively, vs 1/50 in controls), centrilobular cell enlargement (M:13/50 and 20/50, respectively, 6/50 in controls). pericholangitis (Minimal: M: 12/50 and 26/50, respectively, vs 7/50 in control; F: 8/50 and 31/50, respectively, vs 1/50 in controls), brown pigment in Kupffer cells (M: 10/50 and 19/50, respectively, vs 0/50 in controls; F: 8/50 and 24/50, respectively, vs 1/50 in controls), and bile duct hyperplasia (Minimal: M: 11/50 and 23/50, respectively, vs 3/50 in controls, F: 8/50 and 31/50, respectively vs 1/50 in controls). At 1800 ppm, there was an increase in basophilic hepatocytes (F: Moderate: 13/50 vs 4/50 in controls; Marked: 17/50 vs 0/50 in controls). In addition, there were increases in granulomatous inflammation (M: 9/50 vs 0/50 in controls), an increase in the severity of basophilic hepatocytes (Marked: F: 17/50 vs 0/50 in controls) and an increased incidence of generalized cell enlargement (F: 15/50 vs 1/50 in controls). There was also an increase (33/50 vs 4/50 in controls) in the number of animals with minimal testicular interstitial cell hyperplasia. Changes in seminal vesicle secretion, prostate and tubular atrophy were less clearly related to treatment. **Since there was no increase in liver enzyme levels and the non-neoplastic changes in the liver and testes of rats were minimal, the CARC concluded that the effects on these organs were not severe.**

In females, the non-neoplastic findings noted at 1800 ppm consisted of luminal dilatation of uterus (8/50 vs 2/50 in controls), dilated cystic ovarian bursae 5/50 vs 1/50 in controls), and galactoceles (8/50 vs 3/50 in controls) in the mammary glands. **However, the incidences of these findings were skewed because not all the animals in the 200 and 600 ppm dose groups were examined.**

There were decreased body weight gains seen at 1800 ppm (24-30% males; 27-65% females) and 600 ppm (7-15% males; 24-32% females) throughout the study, with smaller decreases in food consumption (ranged from 72%-84% and 83%-98% of controls in males and females, respectively). Systemic toxicity was seen at all doses in this study, based on increased methemoglobin (33-45% at 200 ppm) and related effects on the blood and other organs, including reduced red blood cells, packed cell volume, increased spleen weights, hemosiderosis in the spleen (males), and brown pigment (probably hemosiderin) in the kidneys (females). At the 600 and 1800 ppm, further dose

dependent changes in these measures, as well as increased BUN and decreased triglycerides were noted. At 1800 ppm, sciatic nerve degeneration was also noted.

D. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing at 600 ppm was adequate and the highest dose (1800 ppm) was considered by the CARC to be excessive in female rats based on decrease in body weight gain (42% decrease compared to controls at week 13) and a marked increase in MeHb level (range: 106%-196% increase over the course of study) in female rats. **There was a difference of opinion among Committee members regarding whether the highest dose in male rats was adequate or excessive**. Decreased body weight gains (30% decrease compared to controls at week 13) and a marked increase in methemoglobin level (MeHb; range: 84%-132% increase over the course of study) were considered by some Committee members to be indicative of excessive toxicity while the remaining members were of the opinion that despite these changes, there were no clinical signs of toxicity and the survival of the animals was not adversely affected. MeHb level increased at $200 ppm in females and at $600 ppm in males. Anemia was noted in both sexes and occurred in a dose-related manner. At 1800 ppm, it was more severe in females compared to males based on significant decreases in hematocrit (13%-22% vs 6%-9% in males), hemoglobin (15%-22% vs 8%-10% in males) and RBC (18%-23% vs 9-15% in males) and increased MeHb (106%-196% vs 84%-132% in males). There was a significant decreasing trend in mortality with increasing doses of propanil in male and female rats at 1800 ppm. [The apparent increase in the number of surviving rats at the highest dose was due to fewer deaths in this dose group]. Survival was adequate in both sexes; all dose groups and controls had > 35% survival at study termination.

2. Carcinogenicity Study in CD-1 Mice

Reference: Weatherholtz W. (1983) 24 Month dietary oncogenicity study in Mice. Hazelton Laboratories, America, Inc. Study No. 417-400. dated 12/2/83. **MRID 00155215**

A. Experimental Design

In a mouse carcinogenicity study, CD-1 mice (60/sex/dose) were fed diets containing 0, 5, 30 or 180 ppm of propanil (0.71, 4.39, or 26 mg/kg/day, males; 0, 0.88, 5.35, or 32.4 mg/kg/day, females) for 24 months.

B. Discussion of Tumor Data

No treatment-related increase in tumors was observed in this study.

C. Non-Neoplastic Lesions:

Increased incidence of centrilobular hepatocytic enlargement was noted in 180 ppm dose males. No other treatment-related increases in non-neoplastic lesions were seen.

D. Adequacy of the Dosing for Assessment of Carcinogenicity:

The NOAEL for systemic toxicity was established at 30 ppm, based on increased incidence of centrilobular hepatocytic enlargement in males at 180 ppm (LOAEL). The EPA reviewers concluded that the highest dose level tested was inadequate to assess the carcinogenic potential of propanil in mice.

3. Carcinogenicity Study in Crl:CD-1 (ICR) BR Mice

Reference: Tompkins E. (1994). 24- Month Dietary Oncogenicity Study in Mice with Propanil. Wills Research Laboratories, Inc. Lab Study No. WIL-141011, dated 9/9/94. **MRID 43391701**

A. Experimental Design

In another mouse carcinogenicity study, propanil (97.1% w/w, a.i.) was administered to 80 Crl:CD-1 (ICR) BR mice/sex/dose in the feed at dose levels of 0, 500, or 1000 ppm [0, 74.9 or 150 mg/kg/day for males and 0, 88.6 or 174 mg/kg/day for females, respectively] for up to 104 weeks. Of the total of 80 treated animals/sex/dose, 20 mice/sex/dose were sacrificed at week 52.

B. Discussion of Tumor Data

There were no compound-related tumors observed in male mice. Female mice had a statistically significant increasing trend at $p < 0.01$, and a statistically significant increase in the incidence of malignant lymphomas (all sites) in the pair-wise comparison of the 1000 ppm dose group with the controls at $p < 0.05$. The data are shown in Table 5. It should be noted that while the lymphomas were detected in various tissues, the lymphomas of the spleen were found in all females found dead or euthanized *in extremis*, and lymphoma was reported as the cause of death in these mice. One mouse each in the control and 1000 ppm groups had malignant lymphomas, but not in the spleen.

Table 5. Malignant Lymphoma (All Tissues) Tumor Rates+ in CD1 Female Mice and Exact Trend Test and Fisher's Exact Test Results (p values) (Brunsman, 2001)

	Dose (ppm)		
	0	500	1000
Malignant Lymphoma incidences	4/78 (5%)	4/78[A] (5%)	13/77 (17%)
p =	0.008**	0.640	0.017*

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 34.
A- First malignant lymphoma observed at week 34, dose 500 ppm.
Note: Significance of trend denoted at control; Significance of pair-wise comparison with control denoted at dose level; If *, then $p < 0.05$. If **, then $p < 0.01$.

The registrant provided historical control data from a variety of sources (MRID 43677801). Those most relevant to the study, from the performing laboratory, were limited to one 24 month study, where the incidence of malignant lymphomas in female CD-1 mice was 11.5%, and four 18 month studies, where the incidence ranged from 3.6%-8.3%. The 17% incidence noted in the 1000 ppm female CD-1 mice in this 24 month study was outside those ranges. Other sources cited by the registrant, published between 1982-1995, from different laboratories, showed a range from 0%-28%.

There was an increase in the incidence of malignant lymphomas from controls in the high dose group only. This increased incidence (17%) was outside of the performing laboratory's 18-month historical control data (range: 3.6%-8.3%) but closer to the one historical control value for 24 months (11.5%). Usually the CARC prefers historical control data from the performing laboratory of same study duration and performed within two years of the study under review. In this case the historical control data from the performing laboratory was based on only <u>one</u> study of comparable duration of 24 months. The historical control data from 4 other studies from the same laboratory was for 18 months. Therefore, the CARC considered historical control data cited by the registrant, published between 1982-1995, from different laboratories which ranged from 0%-28%. The incidence of 17% at the high-dose was within this historical control range. Moreover, this tumor occurs spontaneously in this sex and strain of mice. Therefore, the finding of malignant lymphomas at the high-dose was considered by the CARC to have a limited impact on the overall conclusion regarding the weight-of-the-evidence for the carcinogenic potential of propanil.

C. <u>Non-Neoplastic Lesions</u>

No non-neoplastic lesions were observed in this study. However, in females given 1000 ppm, significant increases in absolute (62%) and relative (65%) spleen weights were observed at 52 weeks. Smaller increases at 500 ppm were seen, but did not achieve statistical significance. The principal toxic effects seen in this study were large and statistically significant increases in methemoglobin in both sexes at 1000 ppm (11-17 fold, males; 9-11 fold females) and in males at 500 ppm(6-11 fold); in females at 500 ppm the increase was roughly 6 fold, but due to large variability, it lacked statistical

significance. Blue coloration of the extremities was also seen in both sexes at both doses, probably as a result of increased MeHb. Increased spleen weights (62%) in high dose females were noted earlier. A number of other hematological changes, namely increased reticulocytes and MCV were also noted in the 1000 ppm males, and increased Heinz bodies in males at both doses.

D. Adequacy of Dosing for Assessment of Carcinogenicity

Survival was adequate in all dose groups, and control mice had > 50% survival at study termination. Male and female mice showed no significant incremental changes in mortality with increasing doses of propanil (Brunsman, 2001). There was an increase in spleen weights (62%) in high dose females and, in addition to significant increases in methemoglobin in both sexes at 1000 ppm (11-17 fold, males; 9-11 fold females), a number of hematological changes were observed. These included increased reticulocytes and MCV in the 1000 ppm males, and increased Heinz bodies in males at 500 and 1000 ppm doses. There were no treatment related adverse effects on the body weight gain or non-neoplastic histopathological findings. . A NOAEL for systemic toxicity was not established in this study. A LOAEL of 500 ppm was established, based on significantly increased MeHb levels in males at 52 and 104 weeks and increased levels of Heinz bodies at 104 weeks. A dose-related increase in the incidence of animals with blue coloration of the extremities was observed at$500 ppm in both sexes. **CARC concluded that the dosing at 1000 ppm was adequate and not excessive in both sexes** because there were no treatment related adverse effects on the body weight gain, non-neoplastic histopathological findings or survival of the animals. However, there was increase in MeHb levels, relative spleen weights and blue coloration of extremities in both sexes.

IV. TOXICOLOGY

1. Metabolism

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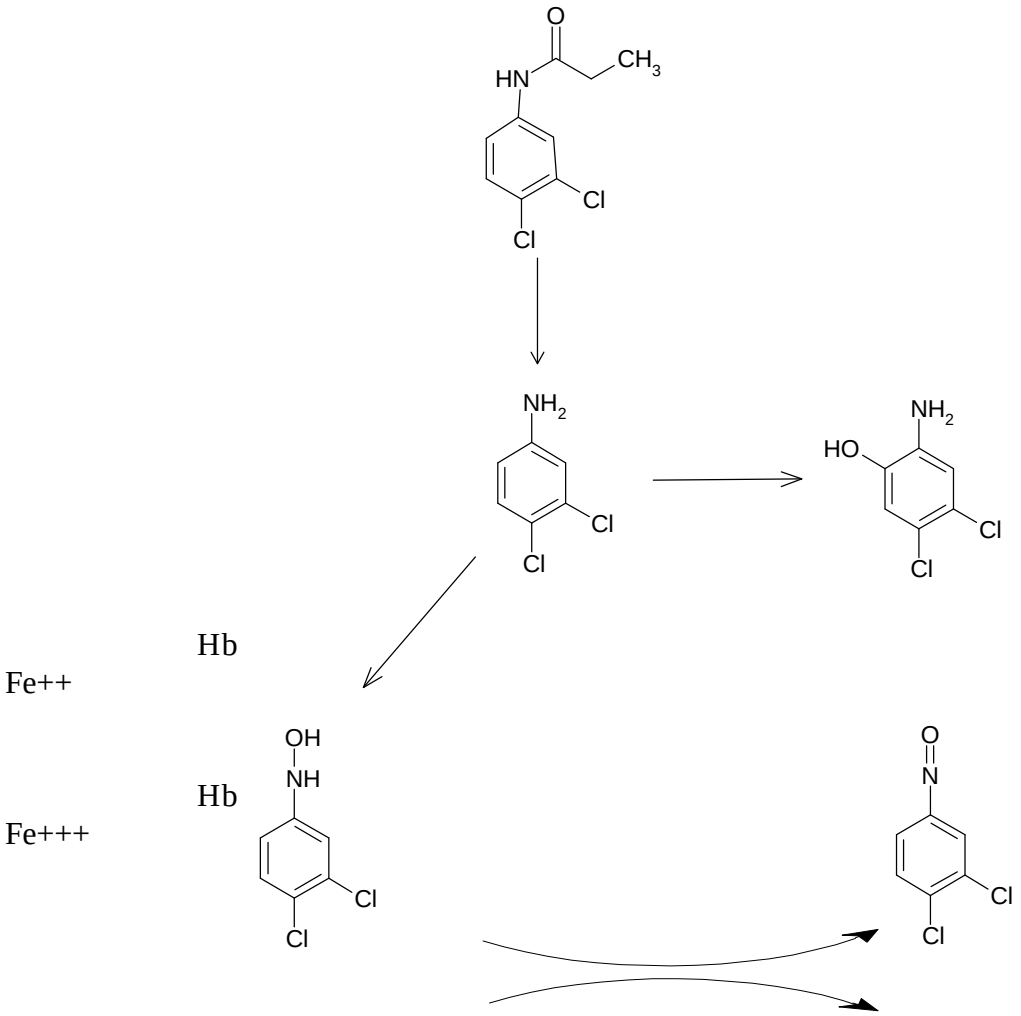
In an acceptable metabolism study (MRID 41796400, 02) groups of CRL:CD(SD) BR 5 rats were given C^{14} labelled propanil or: vehicle (2 rats); a single oral dose of 2.5 mg/kg; a single high oral dose of 300 mg/kg; 14 oral doses of 2.5 mg/kg; or one I.V. dose of 0.7 mg/kg. Urine and feces were collected cumulatively over 4 time periods on the day of dosing, over 2 periods on day 2, and daily thereafter for 7 days. Animals were then sacrificed and their tissues analyzed for radioactivity. Majority of radioactivity (78-90%) was excreted in the urine, and 2-13% in the feces. Most of the radioactivity was eliminated within 24 hours for all except the high oral dose where it took 48 hours to eliminate 90%. For the i.v. data, females excreted 10% in the feces, while males excreted 2%. Carcass contained 0.18-0.71% of the radioactivity, with the liver having the highest residue.

Of the total of 13 metabolite identified, three major metabolites accounted for 17-44% of the radioactivity and were involved in hydroxylation and oxidation of the propanamide moiety. Other metabolites included 3,4 dichloroaniline, and its N-hydroxy and 6-hydroxy derivatives, which are associated with methemoglobin formation.

McMillan et al. (1990a) examined the metabolism of propanil and 3,4-dichloroaniline in rat liver microsomes. The major pathway of propanil metabolism in microsomal incubations was acylamidase-catalyzed hydrolysis to 3,4-dichloroaniline. Oxidized metabolites were identified as 2'-hydroxypropanil and 6-hydroxypropanil. Major microsomal metabolites of 3,4-dichloroaniline were 6-hydroxy-3,4-dichloroaniline and N-hydroxy-3,4-dichloroaniline. N-hydroxy-3,4-dichloroaniline was at least an order of magnitude greater than that of 6-hydroxy-3,4-dichloroaniline in producing methemoglobin.

Propanil (3,4-dichloropropionanilide) also has been reported to be contaminated with the cytochrome P450 enzyme inducers 3,3',4,4'-tetrachloroazobenzene (TCAB) and 3,3',4,4'-tetrachloroazoxybenzene (TCAOB), which are structural analogs of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), and have been associated with chloracne from propanil exposure. McMillan et al. (1990b) determined if treatment of rats with TCAB, TCAOB, propanil, 3,4-dichloroaniline, TCDD, or phenobarbital induced the hepatic microsomal metabolism of propanil and 3,4-dichloroaniline. Acylamidase-catalyzed hydrolysis of propanil to 3,4-dichloroaniline was not induced by any of the pretreatments. However, hydroxylation of propanil at the 2'-position was induced by TCDD, TCAB, TCAOB, propanil, and 3,4-dichloroaniline pretreatments. Ring- and N-hydroxylations of 3,4-dichloroaniline were induced by TCDD, TCAB, TCAOB, and 3,4-dichloroaniline pretreatments. Propanil- ad 3,4-dichloroaniline may be weak inducers of cytochrome P450 isozymes. Propanil undergoes hydroxylation to form N-hydroxyaniline which oxidizes hemoglobin to form methemoglobin. The metabolism of propanil and resulting reactions involved in methemoglobin formation are presented in figure 1.



2. Mutagenicity

Seven acceptable genetic toxicology studies with propanil have been submitted to the Agency. Propanil was not mutagenic in bacteria or in cultured mammalian cells. There was also no indication of a clastogenic effect up to toxic doses *in vivo*. Propanil did, however, cause DNA damage in a DNA repair-deficient strain of *B. subtilis* but not in the pol A^- strain of *E. coli*. The relevance,

therefore, of this positive result in *B. subtilis* is unclear since DNA damage was not manifested as point mutations in microbial systems or mammalian cells, mitotic recombinations in yeast, DNA damage in mammalian cells or chromosomal aberrations in whole animals.

The submitted test battery satisfies the Pre-1991 mutagenicity initial testing battery guidelines. No further testing is required at this time. Findings from these 7 studies are summarized below.

GENE MUTATIONS

1) *Salmonella typhimurium/ Escherichia coli* reverse gene mutation assay (MRID No. 00028625): Propanil was **negative** in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 and in *E. coli* WP2 up to cytotoxic doses ($1,000 :g/plate +/-S9) in independent trials.

2) *Salmonella typhimurium/ Escherichia coli* reverse gene mutation assay (MRID No. 00028625): Independent trials were **negative** in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 and in *E. coli* WP2 up to cytotoxic doses ($1,000 :g/plate +/-S9).

3) Chinese Hamster Ovary (CHO)/HGPRT cell forward gene mutation assay (MRID No. 00155084): Independent tests were **negative** up to cytotoxic doses without S9 activation (125 :g/mL) and with S9 activation (175 :g/mL).

CHROMOSOME ABERRATIONS

4) *In vivo* bone marrow cytogenetic assay (MRID No. 00155083): The test was **negative** in CD-1 male mice administered 0, 26.5, 106, or 265 mg/kg/day by oral gavage once or once daily for 5 consecutive days. Doses selected for this study represented 1/4, 1/10 or 1/40 of the acute LD_{50}, respectively. Overt toxicity was manifested as decreased spontaneous motor activity, lethargy and piloerection in animals receiving $106 mg/kg/day in both dosing regimens. No data were provided to support the claim of decreased metaphases in the high dose animals, and this deficiency

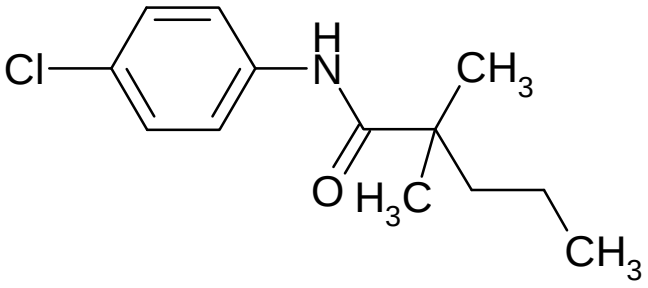
compromised the acceptability of the study. However, since there was a clear indication of toxicity to the test animals, and no differences in LOAELs between male and female mice were seen in the subchronic or chronic studies, the doses should be considered adequate.

OTHER MUTAGENIC MECHANISMS

5) *E. coli/Bacillus subtilis* DNA damage/repair assay (MRID No. 00028625): Propanil was **negative** for differential cytotoxicity in *E. coli* strains W3110/p3478 (pol A +/-) up to an equivalent

cytotoxic dose (5 ：g - S9) but was **positive** for the induction of preferential inhibition of repair-deficient *B. subtilis* M45 (rec-) at 0.01-5 ：g without S9: S9 activation was not included in this study.

6) *Saccharomyces cerevisiae* D3 mitotic recombination assay (MRID No. 00028625): Propanil was **negative** for the induction of mitotic recombinants at doses up to 0.1 % with or without S9 mix.. Independent trials were performed.

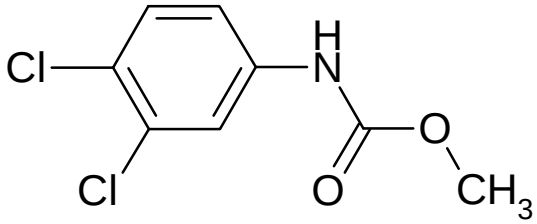


7) Unscheduled DNA synthesis (UDS) in WI-38 human fibroblasts assay (MRID No. 00028625): Propanil was **negative** up to an insoluble level (1000 µg/mL).

3. Structure-Activity Relationships

There were no data on the carcinogenicity and mutagenicity of the three related acylated aniline pesticides, **SWEP** (PC 84601), **Monalide** (PC 28840) and **Solan** (PC 20901)**.** Their structures are presented below.

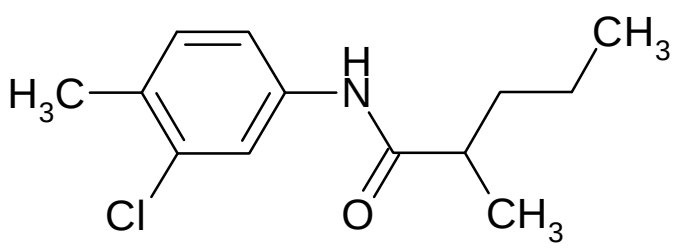
SWEP



Monalide

Solan

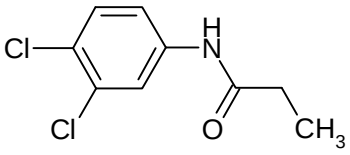
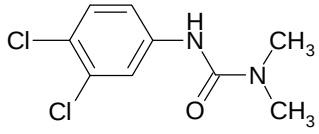
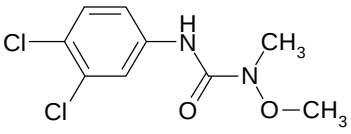
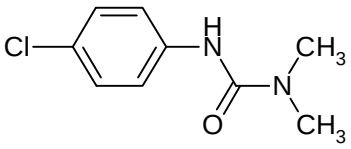
Para-chloroaniline and urea compounds such as diuron, monouron and linuron are also structurally-related to propanil. Para-Chloroaniline hydrochloride(CAS 20265-96-7) was tested by NTP (1989), and was found in water gavage studies to produce clear evidence of carcinogenic activity in male F344/N rats that had uncommon sarcomas of the spleen; pheochromocytomas of the adrenal gland may also have been associated with exposure. Evidence in females for these tumors was equivocal. There was some evidence of carcinogenicity for male B6C3F1 mice that had hepatocellular neoplasms and hemangiosarcomas of the liver or spleen.



Three chlorinated substituted urea herbicides related to Propanil have been identified. These compounds metabolize slowly compared to aniline compounds but do cause methemoglobinemia. The carcinogenic and mutagenic potential of these compounds is presented in Table 7.

Table 7. Structural Analogues of Propanil

Name	Structure	Effect

Propanil PC Code 028201 CAS # 709-98-8		SD Rats: testicular interstitial cell adenomas; liver adenomas(&s); CD1 mice: malignant lymphomas (&s). Non mutagenic in various assays
Diuron PC Code 035505 CAS # 330-54-1		a "known/likely" human carcinogen by all routes, based on urinary bladder carcinomas in both sexes of the Wistar rat, kidney carcinomas in the male rat (a rare tumor), and mammary gland carcinomas in the female NMRI mouse. Mutagenic in cytogenetic assay; negative in other assays
Linuron PC Code 035506 CAS # 330-55-2		Group C carcinogen without quantification Hepatocellular adenomas in female CD-1 mice and testicular adenoma/hyperplasia in male Crl:CD (SD) BR Sprague-Dawley rats. Negative in various mutagenicity assays
Monuron 035501 150-68-5		IARC lists it as Group 3, not classifiable as to humans; limited evidence in animals. Dose related increases of renal and liver cell tumors in male rats; no effects seen in an adequate mouse study. .Nonmutagenic in Ames assay

4. Subchronic and Chronic Toxicity

For repeated exposures of different species to propanil for varying lengths of time leads characteristically to the development of methemoglobinemia. The methemoglobinemia results in the

development of hemolytic anemia, which is associated with decreases in some or all of the following parameters: hemoglobin, RBC count and packed cell volume (hematcrit). Hematological and histopathological evaluations also revealed Heinz bodies in RBCs and hemosiderin deposits in the spleen and kidneys. Increased spleen weights were also noted. These studies are summarized below.

(a) Subchronic

In a subchronic feeding study (1961), 10 Wistar albino rats/sex/pose were exposed to 0, 100, 330, 1000, 3300, 10,000 , or 50,000 ppm of propanil in the diet (MRID 46259, 15419; HED Doc. No. 007559). All rats receiving 50,000 ppm died. At 10,000 and 3300 ppm, there was reduced body weight and food consumption, increased relative spleen weights, decreased hemoglobin, but no compound related histopathological changes were seen. Increases in neutrophils were seen at all doses in females and 1000 and 10,000 ppm in males. Increased relative heart weights in both sexes, and relative testes weight in males at 10, 000 ppm was seen. The LOAEL was 1000 ppm, based on increased relative spleen weights in females, and decreased hemoglobin in males. The study was rated supplementary because of lack of individual animal data.

In an acceptable su bchronic mouse study [MRID 40402901], groups of 10/sex/dose COBS-CD1 Charles River mice received 0, 25, 200, 1600, or 12,800 ppm in the diet for 13 weeks. This study demonstrated toxicity at 1600 and 12800 ppm, including cyanosis (bluish-gray discoloration of the ears and skin), increased mixed function oxidase activity, significantly increased absolute and relative spleen weights in both sexes, significantly increased relative liver weights in females, increased extramedullary hematopoiesis, and hemosiderin in the spleen, and increased hepatocytic pleomorphisms. Additionally, at 12,800 ppm, food consumption was increased and body weight decreased and red blood cells counts were decreased. The study LOAEL was considered 200 ppm, based on 3/10 hepatocytic pleomorphisms in females, and 1 observation of multifocal hepatocytic necrosis in a male.

(b) Chronic

The chronic toxicity of propanil has been evaluated in long-term feeding studies in the rat, mouse and dog.

In the rat study (MRID 43303201), a significant decrease in body weight gain was observed at 600 and 1800 ppm in males and females throughout the entire 24-month study period. The decreases in body weight gains correlated to some degree with decreased food consumption. There were treatment related non-neoplatic lesions in the liver, testes, and female reproductive organs. These changes are discussed earlier on page 5.

In CD-1 mice, in addition to significant increases in methemoglobin in both sexes and increased spleen weights were noted in females following long-term dietary administration of propanil (MRIDs 00155215 and 43391701). The NOAEL for systemic toxicity was established at 30 ppm,

based on increased incidence of centrilobular hepatocytic enlargement in males at 180 ppm (LOAEL; MRID 00155215). In a recent study, no treatment related non-neoplastic lesions were observed Crl:CD-1 (ICR) BR mice fed propanil for 104 weeks. However, in female mice given 1000 ppm, significant increases in absolute (62%) and relative (65%) spleen weights were observed at 52 weeks. Smaller increases at 500 ppm were seen, but did not achieve statistical signficance. A NOAEL for systemic toxicity was not established in this study. A LOAEL of 500 ppm, was established based on significantly increased MeHb levels in males at 52 and 104 weeks and increased levels of Heinz bodies at 104 weeks. A dose-related blue coloration of the extremities was observed at $500 ppm in both sexes. Refer to page 8 and 9 for details.

In a one year dog study [MRID 42962901], a dose-dependent increase in methemoglobin formation was observed, and graded as moderate to severe at the two highest dose levels (1600 and 3200 ppm). Hematological evaluation also revealed decreases in RBC count, hemoglobin, packed cell volume and mean cell hemoglobin concentration; reticulocyte smears showed increased incidences of Heinz body formation. Brown pigmentation (hemosiderin) was found in the bone marrow, kidney and liver of both sexes; the grade and incidence of hemosiderin deposits were dose-related. Increased BUN, creatinine, and potassium were seen at the high dose, as well as increased liver weights and thyroid weights. Decreases in body weight gain and food consumption at the high dose in both sexes were seen early in the study, but did not persist. No NOAEL was identified.

5. Mode of Action Studies

No mode of action studies related to carcinogenicity have been identified. Propanil causes anemia by forming MeHb in a variety of species including rats, mice, dogs (refer to Pages 15-17) and humans (DeSilva and Bodinayake, 1997 and Yamazaki et al., 2000). The mode of action for methemoglobinemia involves hydroxylation of propanil to form N-hydroxyaniline, an active metabolite, which oxidizes hemoglobin to form MeHb.

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

1. Carcinogenicity

The CARC concluded that:

- **In a combined chronic toxicity/carcinogenicity study in Sprague-Dawley rats, there was treatment-related increase in testicular adenomas in males** because:

1) There was a statistically significant ($p<0.01$) positive trend and a statistically significant ($p< 0.05$ or $p< 0.01$) increase by pair-wise comparisons of the 600 and 1800 ppm (28 and 88 mg/kg/day, respectively) dose groups with the controls for testicular interstitial cell adenomas (21% and 72%, respectively, vs 8% in controls). The increase in the incidence of testicular tumors in both the 600 and 1800 ppm dose groups was dose-dependent and was outside the range for the historical controls (0%-11%). At 1800 ppm, there was an increase in the incidence of minimal hyperplasia of the testes. (33/50 vs 4/50 in controls). 2) Among female rats, there was a statistically significant ($p<0.01$) positive trend and a statistically significant ($p< 0.05$) increase by pair wise comparison of the 1800 ppm (145 mg/kg/day) dose group with the controls for liver adenomas (13% vs 3% in controls). The incidence of liver adenomas was outside the range for the historical controls (0%-2%). These changes were accompanied by non-neoplastic changes in the liver which were not severely adverse. However, CARC considered that these tumors occurred at an excessively toxic dose that produced 42% decrease in body weight gain at 13 weeks and 106%-196% increase in MeHb level over the course of study in females. 3) For females, there was also a statistically significant borderline increasing trend for endometrial polyps. Although there was an increased incidence of polyps at 600 and 1800 ppm (8% and 13%, respectively vs 4% in controls), the increases were not statistically significant by pair wise comparisons with the controls. The increased incidence of endometrial polyps was considered by the CARC to be skewed since not all animals in the 200 and 600 ppm dose groups were examined microscopically. Moreover, the endometrial polyps are not tumors but are considered simply as a proliferative response of the endometrium to the damaging effects of steroid sex hormones.

There was a difference of opinion among Committee members regarding whether the highest dose in male rats was adequate or excessive. The decreased body weight gains (30%) and a marked increase in MeHb level (range: 84%-132% increase over the course of study) were considered by some of the Committee members to be indicative of excessive toxicity while the remaining members were of the opinion that despite these changes, there were no clinical signs of toxicity and the survival of the animals was not adversely affected. For female rats, the liver changes observed were not severely adverse based on lack of increase in liver enzyme levels and minimal non-neoplastic liver changes. However, the highest dose was considered to be excessive based on decreased body weight gains (42%) and a marked increase in MeHb level (range: 106%-196% over the course of study). Anemia was noted in both sexes and occurred in a dose-dependent manner. At 1800 ppm, it was more severe in females compared to males based on significant decreases in hematocrit (13%-22% vs 6%-9% in males), hemoglobin (15%-22% vs 8%-10% in males) and RBC (18%-23% vs 9-15% in males) and increased MeHb (106%-196% vs 84%-124% in males). Survival of the animals was not affected by the treatment.

The CARC concluded that the increases in testicular tumors in male rats were treatment-related.

- **In a combined chronic toxicity/carcinogenicity study in female Crl: CD-1 (ICR) BR mice, there was an increase in malignant lymphomas, a common fatal tumor** because: 1) There was a statistically significant ($p<0.01$) positive trend for malignant lymphomas (all sites). There was also a statistically significant ($p<0.05$) increase by pair wise comparison of the 1000 ppm (174 mg/kg/day) dose group with the controls for malignant lymphomas (17% vs 5% in controls). There was an increase in the incidence of malignant lymphomas from controls in the high dose group only. This increased incidence (17%) was outside of the performing laboratory's 18-month historical control data (range: 3.6%-8.3%) but closer to the one historical control value for 24 months (11.5%). Usually the CARC prefers historical control data from the performing laboratory of same study duration and performed within two years of the study under review. In this case the historical control data from the performing laboratory was based on only <u>one</u> study of comparable duration of 24 months. The historical control data from 4 other studies from the same laboratory was for 18 months. Therefore, the CARC considered historical control data cited by the registrant, published between 1982-1995, from different laboratories which ranged from 0%-28%. The incidence of 17% at the high-dose was within this historical control range. Moreover, this tumor occurs spontaneously in this sex and strain of mice. Therefore, the finding of malignant lymphomas at the high-dose was considered by the CARC to have a limited impact on the overall conclusion regarding the weight-of-the-evidence for the carcinogenic potential of propanil. No tumors were seen in male mice.

  The highest dose level tested for the male and female mice was considered by the CARC to be adequate and not excessive because there were no treatment related adverse effects on the body weight gain, non-neoplastic histopathological findings or survival of the animals. However, there was increase in MeHb levels, relative spleen weights and blue coloration of extremities in both sexes.

2. Mutagenicity

   The CARC concluded that propanil was negative for genotoxic potential in a battery of acceptable mutagenicity studies which satisfy the pre-1991 FIFRA guideline requirements. These studies included reverse gene mutation assays in bacteria, Chinese Hamster Ovay cell forward gene mutation assay, chromosome aberration assays, UDS assay and DNA damage/repair assay. No new studies were requested by the CARC.

3. <u>Structure-Activity Relationships</u>

Structurally related compounds including p-chloroaniline, monouron, diuron, and linuron cause liver and in some cases testicular tumors (e.g.linuron) in rats. These compounds are nonmutagenic.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the CARC classified propanil into the category **"Suggestive evidence of carcinogenic potential by all routes of exposure, but not sufficient to assess human carcinogenic potential."** There was an increase in benign tumors in male rats. But considering the non-mutagenicity of propanil the available evidence for carcinogenicity did not reach the level of concern associated with category "Likely to be carcinogenic in humans". The Committee's decision was based on the following weight-of-the-evidence considerations:

1. Propanil induced testicular interstitial cell adenomas in male rats. The hepatocellular adenomas in female rats occurred only at an excessively toxic dose. The increase in commonly occurring malignant lymphomas in female mice added little to the overall weight of evidence for the carcinogenic potential of propanil.

2. Propanil was not mutagenic.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

The dose-response assessment is not indicated for agents when the evidence is "suggestive".

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